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The Treatment of Malignant Tumors by the Toxins of the Streptococcus of Erysipelas.

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THE TREATMENT OF MALIGNANT TUMORS BY THE TOXINS OF THE STREPTO- COCCUS OF ERYSIPELAS.

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It has been known for a long time that in exceptional cases an attack of erysipelas has exerted a curative effect on malignant tumors. A number of years ago Billroth reported a case of inoperable sarcoma of the pharynx cured by a severe attack of facial erysipelas. The tumor mass sloughed and the large defect healed rapidly by granulation, leaving a healthy scar upon the site occupied by the tumor. Isolated cases of this kind have been reported from time to time, but the diagnosis was not always established by sufficiently careful clinical observations and microscopic examination of the tumor tissue. The discovery of the microbe of erysipelas by Fehleisen, and the cultivation of the streptococcus upon artificial nutrient media outside of the body enabled investigators to produce erysipelas artificially in the uncomplicated form in man and the lower animals. As soon as it was demonstrated experimentally that simple uncomplicated erysipelas is a disease attended by but little danger to life, the suggestion was made that, if the disease could be artificially produced in man by inoculation with pure cultures, the local and general conditions thus produced might prove useful in the cure or amelioration of inoperable malignant tumors. Of seven persons the subjects of malignant tumors, inoculated by



Fehleisen with pure cultures, six developed typical erysipelas; in the seventh case the patient had passed through an attack of erysipelas only a few weeks previously and was, in all probability, still protected against a new attack. This patient was inoculated a second time with a negative result. Fehleisen has seen, by this treatment, a cancer of the breast become smaller, while a case of fibro-sarcoma and another of sarcoma were not materially affected by this method of treatment.

Janicke and Neisser have recorded a death from the erysipelas thus intentionally produced, in a case of cancer of the breast beyond the reach of an operation. At the post-mortem it was shown that the tumor had almost completely disappeared, and the microscopic examination of portions that had remained appeared to prove that the tumor cells had been destroyed through the direct action of the microbes.

Biedert saw in a child suffering from a sarcoma, involving the posterior part of the cavity of the mouth and pharynx of the left half of the tongue, the nasopharyngeal space and the right orbit, the tumor disappear almost completely during an attack of erysipelas.

Kleeblatt reports the case of a lympho-sarcoma followed by infection of the cervical glands, in which the tumors diminished markedly in size under the influence of an inter-current attack of erysipelas, but resumed its former malignant tendencies as soon as the disease had subsided. The patient was afterward intentionally inoculated with a pure culture of the streptococcus of erysipelas, but the beneficial effect was, as before, only a temporary one, as the tumors steadily increased in size, the patient dying of exhaustion. In another somewhat similar case, the inoculation caused a typical attack of erysipelas, under the influence of which the tumor rapidly disappeared.

Cases, on the other hand, have been reported in which, after an accidental or intentional attack of erysipelas, the malignant tumor began to grow more

rapidly. Neelsen describes a case of carcinoma of the breast in which, after two severe attacks of erysipelas, the tumor not only began to grow faster, but at the same time regional infection progressed more rapidly.

Bruns gives an account of the effect of erysipelas on tumors in twenty-two patients. Among these, three cases of sarcoma were permanently cured. Two cases of multiple keloid after burns were also permanently benefited. In four cases of lymphoma of the neck, some of the glandular swellings disappeared completely and some were reduced in size. In three cases of carcinoma of the breast, one was not influenced by the treatment, in one the tumor was diminished one-half in size, and in the third it contracted to the size of a pea, in which condition it remained at the time the report was made. A multiple fibro-sarcoma was greatly benefited, while an orbital sarcoma was not improved.

Spraenth concludes as the result of his observations that the products of the erysipelatos inflammation in certain cases can act in a curative manner upon malignant growths. He injected subcutaneously at a point distant from the tumor the sterilized toxic products of the microbes of erysipelas. Improvement and even complete disappearance of the tumors followed, although recurrence usually took place. The effect was much more marked in sarcoma than in carcinoma.

Burch observed that as a result of accidental or intentional infections with the microbe of erysipelas, tumors such as sarcoma disappeared by fatty degeneration.

Janicke and Neisser demonstrated by microscopic examination that cancer cells were actually destroyed by erysipelas streptococci. In view of the uncertainty of the result and the not inconsiderable danger to life which attends the inoculation of live cultures of the streptococcus of erysipelas, in patients debilitated by antecedent disease, it is safe to

predict that this therapeutic resource will be abandoned in the future treatment of malignant tumors.

Coley, of New York, has made the treatment of malignant tumors with live and sterilized cultures of the streptococcus of erysipelas a special study since 1891. In 1893 he reported ten new cases of malignant tumors treated by repeated inoculations with erysipelas. From a study of the literature of this subject at that time it was found that there were recorded thirty-eight cases of malignant tumors in which an attack of erysipelas had occurred, either by accident or intent. In thirty-three cases the erysipelas was accidental and in fifteen it was the result of inoculation. Of seventeen cases of carcinoma, three were permanently cured. Of the seventeen cases of sarcoma, seven were free from recurrence from one to seven years after the attack of erysipelas. Ten cases showed quite marked improvement; one patient died as the result of an accidental attack of erysipelas.

In the summary of the analysis of recorded cases, Coley excluded eight cases of his own, treated by repeated inoculations with erysipelas cultures; in none of these cases did an actual attack of erysipelas result, and yet the inoculations appear to have been followed by marked improvement, and this would indicate that there exists in the cultures some substance which is antagonistic to the tumor growth.

In view of the fact that the artificial production of erysipelas by inoculations with active cultures of the erysipelas microbe is not devoid of risk to life, and that improvement in certain cases followed, by inoculations with live cultures, which did not produce erysipelas; these facts led Coley and others to employ sterilized cultures, which appear to have produced the same therapeutic effects as the active cultures.

It was also ascertained by experiments that the efficiency of the dead cultures is increased by the addition of the bacillus prodigiosus, a comparatively harmless microbe. In a recent article on the treatment of malignant tumors with the toxins of these

two microbes, Coley maintains the efficiency of the mixed dead cultures of these two microbes in the treatment of some cases of malignant tumors, especially sarcoma. In the same publication he reports nine cases of inoperable sarcoma permanently cured by repeated inoculations with the mixed toxins of these two microbes, that came under his own observation, and refers to a few successful cases in the practice of other physicians. The toxins which he uses now are prepared in the following manner:

"Method of Preparation of the Toxins.—To make the toxins of erysipelas and prodigiosus, ordinary peptonized bouillon is put into small flasks, containing 50 to 100 cc., which, after proper sterilization, are inoculated with the streptococci of erysipelas and allowed to grow for three weeks at a temperature of 30 to 35 degrees C. The flasks are then inoculated with bacillus prodigiosus, and the cultures allowed to grow for another ten or twelve days at room temperature. At the end of that time, after being well shaken up, the cultures are poured into sterilized glass-stoppered one-half ounce bottles, and heated to a temperature of 50 to 60 degrees C. for an hour; sufficient to render them perfectly sterile. After cooling, a little powdered thymol is added as a preservative, and the toxins are ready for use. The toxins when prepared in this way are very much stronger than when filtered through a Pasteur, Chamberland or Kitasato filter, the active principles contained in the germs themselves being preserved. If, as is sometimes the case, the preparation is found to be too strong to use with safety, it can be diluted with glycerin or sterilized water.

"The best method of making the bouillon is to soak a pound of chopped lean meat over night in water. In the morning strain it through a cloth, make up to 1,000 cc., and boil for one hour. Then filter through a cloth, add peptone and salt, neutralize and boil again for an hour. The bouillon will then pass through filter-paper perfectly clear, and be ready

to put into the flasks. It is not, however, necessary to neutralize the bouillon, as the streptococci will grow even more readily in acid bouillon, and the resulting preparation is, if anything, stronger than when neutralized bouillon is used.

"In order to keep up the virulence of the cultures they are put through rabbits in the following way: the hair of the ear is clipped close with a pair of scissors, and the skin washed with weak carbolic acid, and then sterilized water. A minute quantity of a bouillon culture, forty-eight hours old, is then injected subcutaneously in four or five different places in the ear. Forty-eight hours later, after again washing the ear with carbolic acid and sterilized water, a flat needle sterilized in the flame is inserted under the skin at or near the point of inoculation, and the layer of the skin cut off with a sharp sterilized scalpel. The piece of skin is then rubbed well over the surface of an agar tube with a thick platinum-wire needle. After twenty-four hours in the incubator the colonies of streptococci will show as minute white specks, and from them a pure culture can be obtained. If the agar is made with 75 per cent. of bouillon and 25 per cent. of urine, the streptococci will grow more freely than if bouillon alone is used. The dose of this preparation varies from 1 to 8 minims; I have had a temperature of 105 degrees F. follow the injection of 2 minims. I usually begin with the minimum dose and gradually increase until the desired reaction, *e. g.*, temperature 103 to 104 degrees F. is reached."

Coley does not say that this treatment is successful in all cases, and reports his failures with his successful cases, but his satisfactory results are out of proportion to those of any other practitioner, in the employment of the same remedy in similar cases. It is generally known that carcinoma has proved more refractory to the toxins of the streptococcus of erysipelas and the mixed toxins than sarcoma.

A distinction should be made between the thera-

peutic action of non-malignant tumors of erysipelas and the subcutaneous injections of sterilized cultures of the microbe of this disease. In erysipelas involving a malignant tumor, the superficial lymphatic channels are the seat of an active inflammation, the product of which always temporarily obstructs the pathways through which local, regional and general infections occur and, in exceptional cases, permanent interruption of the lymph current may limit or arrest the growth of the tumor. No such anatomic changes are produced by the injection of the toxins.

The treatment of inoperable sarcoma and carcinoma with the mixed toxins, as advised and practiced by Coley, has been given a fair trial in the surgical clinic of Rush Medical College, and so far it has resulted uniformly in failure.

The accompanying table is a brief summary of the cases subjected to this treatment.

The injections were made daily, gradually increasing the dose until the desired reaction was produced. In most of the cases the reaction was initiated by a chill, or at least a sense of chilliness. The temperature reached the maximum height in the course of a few hours, and continued from six to twenty-four hours. The toxins used were obtained from three different sources, the last supply directly through the courtesy of Dr. Lambert, of the laboratory of the Cancer Hospital, New York. A temporary swelling and diffuse reddening of the skin at the point of puncture was a common occurrence; abscess formation was seldom observed. Loss of appetite, restlessness and insomnia were some of the general symptoms most constantly produced by the injections, when used in doses large enough to provoke febrile reaction. In all of the cases, the injections failed to effect even temporary improvement, and in some of them the local and general conditions appeared to be aggravated by the treatment. The results of this treatment have been most discouraging in my hands, and although I shall continue to resort to it in other-

wise hopeless cases in the future, I have become satisfied that it will be abandoned in the near future and assigned to a place in the long list of obsolete remedies employed at different times in the treatment of malignant tumors, beyond the reach of a radical operation.

Name.	Age.	Tumor.	Number of injections.	Dose in minims.		Reaction.
				Mini- mum.	Maxi- mum.	
Ross.	35	Multiple melano-sarcoma of breast and sub-clavicular lymphatic glands.	25	3	10	101° F
Nelson. . . .	32	Sarcoma of testicle regional infection of lymphatic glands.	25	3	8	103° F
Sherwood . .	47	Sarcoma of thigh.	30	5	9	103° F
Hickman. . .	50	Recurring sarcoma of shoulder after amputation through shoulder joint for sarcoma of humerus.	110	5	12	104° F
Leichsenring.	48	Fascia sarcoma of back.	40	7	12	102° F
Scott.	36	Carcinoma of penis, infection of lymphatic glands of groin on both sides.	30	7	8	102° F
Young.	55	Sarcoma of mouth.	65	4	12	102° F
Ehrlich. . . .	52	Secondary carcinoma of lymphatic glands of uterus.	25	5	10	103° F
Movius. . . .	45	Carcinoma of uterus.	75	4	15	104° F

